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Hyperuricemia and its Association with the Presence of Metabolic Syndrome among Indonesian Obese Adolescents

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Abstract: Metabolic syndrome (MetS) plays an important role in inflammation and insulin resistance. Increasing number of adolescents MetS were common among obese. The inflammatory biomarkers may contribute to increasing levels of uric acid (UA). Currently UA is not only associated with gout, but also cardiovascular disease. This was a cross sectional study conducted in Semarang City, Indonesia. Consecutive sampling for obese adolescents was administrated. About 81 obese adolescents from two government highs schools were recruited in this study. We measured anthropometry (weight, height, waist circumference, neck circumference), clinical data (systolic and diastolic blood pressure) and biochemical data (triglyceride, HDL-cholesterol, fasting blood glucose, uric acid). A subjects was categorized as MetS if presence 3 or more components of MetS. Gender and Hyperuricemia was associated with presence of MetS ($p = 0.048$ and $p = 0.004$). The mean levels of UA increased accordance to the amount of MetS components ($p = 0.000$). Regression logistic analysis concluded that hyperuricemia as major risk factor of MetS among obese adolescents (OR = 3.97). Hyperuricemia contributed to metabolic syndrome among Indonesian obese adolescents.

Key words: Hyperuricemia, metabolic syndrome, obese adolescents

INTRODUCTION

Obesity and metabolic syndrome have been increased in developing countries (Lloyd *et al*., 2012). Indonesia National Primary Health Survey 2013 indicated significantly increased of obesity in Indonesia adolescents from 1.7% in 2007 to 7.3% in 2013. Central obesity among Indonesian people was also elevated significantly from 18.8% in 2007 to 26.6% in 2013 (Indonesian Basic Health Report, 2013). The incidence of metabolic syndrome (MetS) increases with the increasing incidence of obesity. The condition of metabolic syndrome (MetS) is associated with some inflammatory processes that was characterized by elevation of proinflamator agents e.g., C-Reactive Protein (CRP), Tumor Necrosis Factor-α (TNF-α), Interferon-gamma (IFN-γ), Interleukin (IL)-6 and recently was IL-18 (Thaman and Arora, 2013). Inflammatory biomarkers are then associated with atherosclerotic vascular disease process as comorbidities of metabolic syndrome. Some of studies expected that atherosclerotic vascular disease associated with uric acid (UA) levels, with unclear metabolic disorder as a mediator (Lippi *et al*., 2008).

The normal UA levels function as a neuroprotective agent is already established. However, some studies revealed that high level of uric acid have been associated with atherosclerotic vascular disease, insulin resistance and metabolic syndrome (Nagahama *et al*., 2004). Uric acid levels >5.5 mg/dl has been associated with cardiovascular risk (Feig *et al*., 2008). Hyperuricemia lead to declining of endothelial nitric oxide. Decreasing of endothelial nitric oxide induced vascular proliferation and endothelial dysfunction (Kanellis and Kang, 2005). The association between UA and atherosclerotic vascular disease is still being controverted due to indirect association and the possibility of metabolic syndrome as originator of Hyperuricemia and atherosclerotic vascular disease.

There are five risk factors for metabolic syndrome diagnosis: central obesity by measuring waist circumference, elevated triglyceride levels, decreased levels of HDL (High Density Lipoprotein), increased blood pressure and insulin resistance seen with an increase in fasting blood glucose levels (Grundy *et al*., 2004). Through five risk factors for the metabolic syndrome, the metabolic syndrome diagnosis among children and adolescents were divided into two groups: the pre-metabolic syndrome (Pra-MetS) with 1 or 2 risk factors and metabolic syndrome (MetS) group with ≥3 risk factors (Zimmet *et al*., 2007).

It is already known that atherosclerosis stages have began since children and adolescents (McGill *et al*., 2000). Increasing prevalence of adolescent's metabolic syndrome and obesity may attribute to that condition. The association of single factors or more of metabolic syndrome and Hyperuricemia among obese

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adolescents has never been investigated in developing countries. In spite of many studies documented the relationship between the presences of MetS with UA in adults but still a few studies was observed in children and adolescents in developing countries. This study aimed to examine the association between the presence of metabolic syndrome and Hyperuricemia among obese adolescents.

MATERIALS AND METHODS

Subjects, criteria and anthropometry measurement: This was a cross-sectional study performed between July of 2015 and September of 2015, approved by the Research Committee of Diponegoro University, Faculty of Medicine number 594/EC/FK-RSDK/2015. A convenience sample was used. Inclusion criteria in this study was adolescents aged between 15 and 18 years old. Subjects who had any chronic disease such as secondary hypertension, type 1 diabetes mellitus, diagnosis of inflammatory process, consume alcohol, smokers, or who were using medication that interfered with glucose metabolism or lipids, such as steroids and anti-inflammation, were excluded. A total of 81 subjects were recruited in this study.

Several anthropometry measurement was conducted in this study. Weight was measured using calibrated digital body weight scale (accuracy 0.1 kg). Height was measured using statur meter (accuracy 0.1 cm). Body Mass Index (BMI) was calculated using Weight (kg) divided with Height (m^2). Considering the following categories: obesity (z score + 2 < BMI $\leq$ z score + 3) and severe obesity (BMI > z score + 3), the WHO (2007) reference was pointed out (WHO, 2007). Waist circumference (WC) was measured using non-stretchable tape in the midpoint between the lowest rib and the iliac crest (Klein *et al*., 2007). Neck circumference (NC) was measured using seca® 203 in the middle of the neck, between the middle of the cervical spine and neck anterior mid and subject standing upright (Aswathappa *et al*., 2013). Girls with WC$\geq$90 percentile were considered as having altered WC. This study cutoff 90 percentile levels of WC for girls was 87 cm and boys 93 cm. Cutoff values for NC were obtained from this study (Ferretti *et al*., 2015) which were categorized girls with altered NC>32.65 cm and boys> 37.95 cm.

Measurement of MetS biochemical indicators and uric acid: All subject were informed to do at least 10 h fasting began at 10 am at Indonesia time before bloods collection. Two blood pressure measurements were scaled with 2 min interval using riester® sphygmomanometer and was operated by well-trained general practitioner. The mean of two measurements was considered as the systolic (SBP) and diastolic (DBP) blood pressure values. Well-trained laboratory analyst gripped about 3 cc venous bloods. The DiaSys® Cat No. 20144 reagents was being used in the analysis of the fasting blood glucose. Triglyceride (TG) was analyzed using enzymatic method (Beckman TG Reagent). Magnesium-dextran sulfate precipitation reagent was used to separate HDL cholesterol (HDL-c) from lipid complex. Fasting blood glucose, uric acid, HDL-c and TG were quantified using enzymatic method (Roche Cobas Mira S28-6537, Roche Diagnostics, Swizterland). Biochemical measurement was conducted in accredited laboratory.

Hyperuricemia was considered with values >5.5 mg/dl (Feig *et al*., 2008). The diagnosis of MetS was obtained using the criteria recommended by the National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP) III (NCEP, 2002) adapted to the adolescents, which considers the presence of MetS as at least three of the following items: WC$\geq$90 percentile (girls>87 cm and boys>93 cm); TG$\geq$110 and HDL-c<40 mg/dl, fasting blood glucose $\geq$100 mg/dl, SBP and DBP>125 and 75 mmHg (Tang *et al*., 2010).

Statistical analysis: The data were presented as proportions, means and standard deviations (SD). After applying the Kolmogorov-Smirnoff test to assess for normality, the association of uric acid levels with gender, nutritional status, WC, NC, SBP, DBP, TG, fasting blood glucose, HDL-c and MetS was demonstrated using the chi-squared or Fisher's exact test, when necessary, with a 95% confidence interval (95% CI) and prevalence ratio (PR). The differences levels of uric acid on the number of risk factors of metabolic syndrome were performed using one-way analysis of Variance (ANOVA) test. The results of ANOVA test was continued with Bonferroni's post hoc test.

Logistic-regression was used for variable adjustment, whose criterion for variable inclusion was the association with the dependent variable in the bivariate analysis with p value<0.20. The variables were included in the regression analysis using the 'enter' method, according to the decreasing value of odds ratio. The Hosmer-Lemeshow test was used as a measure of quality-of-fit for the logistic-regression models, in which a p-value$\geq$0.05 indicates that the model is adjusted. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, US).

RESULTS

A total of 81 obese adolescents completed this study. All subjects were taken from two middle-up social economy status high school in Semarang City area. Proportion of females in this study was 49.4% vs. males subject 50.6%, with mean of age 15.77±1.06. Of the 81 subjects, mean of BMI was 30.05±4.95. The prevalence of MetS among obese adolescents was 42.0% (56.1% among males and 27.5% among females). Mean of UA levels in

all subjects was 6.84±2.05 (3.40-13.90), with mean among males subject 7.48±2.30 and females subject 6.19±1.53 (Table 1).

Systolic Blood Pressure was high in 34.6% (28 of 81) and DBP in 54.3% (44 of 81) of the obese adolescents. High levels of Triglyceride were described in 17.3% (14 of 81) among the subjects. Low levels of HDL-C were observed in 70.3% (57 of 81 subjects) among obese adolescents. Hyperglycemia was observed in only 1.2% of the subjects (Table 2). Table 2 represents gender and presence of metabolic syndrome associated with Hyperuricemia. It shows that the risk to have Hyperuricemia was higher in the resulting groups: Males obese (PR = 2.64) and obese adolescents with MetS (PR = 4.68).

The mean concentrations of UA were significantly different between the components of MetS (p = 0.006). They increased with the number of the components of MetS. There was significantly differences between 1 and 2 components of MetS vs. 4 components of MetS (2.11 (95% CI, 0.06-4.16) with p = 0.040 vs. 2.30 (2.65-4.33) with p = 0.018), (Fig. 1). Over multiple logistic regression analysis, it was concluded by observe the final model of regression, only the presence of MetS remained associated with Hyperuricemia among obese adolescents. It was examined that, among obese adolescents with MetS, the possibility of having increased UA levels was almost four times higher than among obese adolescents without the presence of metabolic syndrome; as indicated by the results of the Hosmer and Lemeshow test, the model presented a good fit (Table 3).

Table 1: Waist circumference, neck circumference, blood pressure and biochemical parameters between gender among 81 obese adolescents

Parameters	Males (N = 41)	Females (N = 40)
Waist circumference (WC)[a]	98.58±13.26	89.28±10.24
Neck circumference (NC)[a]	38.38±2.70	34.08±2.07
Systolic Blood Pressure[b]	125 (100-160)	112.5 (90-140)
Diastolic Blood Pressure[b]	85 (80-90)	80 (70-90)
Triglyceride (mg/dl)[b]	83 (57-296)	81.5 (54-130)
HDL Cholesterol (mg/dl)[b]	35 (27-49)	35 (25-49)
Fasting blood glucose (mg/dl)[b]	92 (82-110)	92.5 (78-108)
Uric acid levels (mg/dl)[a]	7.48±2.30	6.19±1.53

[a]Data was presented as mean±SD (the Kolmogorof-Smirnoff p > 0.05). [b]Data was presented as median (minimum-maximum) (the Kolmogorof-Smirnoff p value<0.05)

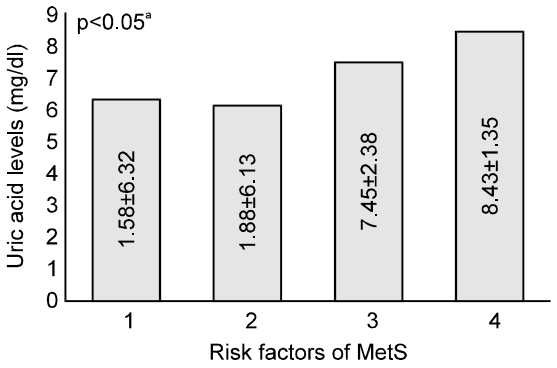

Fig. 1: Mean of uric acid level between risk factors of metabolic syndrome

DISCUSSION

The prevalence of MetS in our results was higher in males compare to females. This result is consistent with Iranian study among children and adolescents that showed the prevalence of MetS among male subjects was 11% vs. female 7% (Rashidi *et al*., 2014). The higher number of MetS among male obese adolescents was also found in previous studies (Sewaybricker *et al*., 2013; Evia-Viscarra *et al*., 2013). This study have also presented that UA levels increased with the number of the MetS components. The result of this study confirms previous result that the prevalence of higher UA levels was higher in the adolescents with MetS (Cardoso *et al*., 2013) and it confirmed that obese adolescents with MetS had higher risk to Hyperuricemia than without MetS.

Consistent with Pacifico *et al*. (2009) demonstrated the association between MetS with UA levels among children and adolescents (Pacifico *et al*., 2009). The difference between our results and Pacifico *et al* (2009) is in the subjects of study. Our study subjects was only obese adolescents and it showed that the prevalence of MetS with hyperuricemia among adolescents was 35.8%, slightly lower compare to 41.6% among children with MetS (Pacifico *et al*., 2009), but higher than Cardoso *et al*. (2013). According to previous study there was an interconnected mechanisms between MetS, proinflammatory reaction and diabetes that may effect to increase UA levels (Baldwin *et al*., 2011; Li *et al*., 2013). It was concluded that underlying factor of insulin abnormalities (e.g. insulin resistance) triggered deliverance of nitric oxide (NO) from endothelial cells. Obesity as underlying risk factor of MetS was decreasing adiponectin and increased inflammatory response in adipose tissue. It will increase Monocyte Chemotactic Protein-1 (MCP-1) which has an important role in insulin resistance development. Having said that, uric acid has reported also increase MCP-1 (Kanda *et al*., 2006).

Uric acid is the final product of purine in humans and in normal value it has the strength to protect cell membrane from lipid oxidation. Hyperuricemia is now commonly associated with factors in MetS e.g., central obesity, hypertriglyceridemia, hypertension and hyperglycemia (Xu *et al*., 2014). The correlation between the concentration of uric acid with abdominal obesity, insulin resistance, hypertension and dyslipidemia are complex and bi-directional (Li *et al*., 2013). Pacifico *et al*. (2009) also showed a significant correlation between uric acid with components of the metabolic syndrome. Uric acid concentrations were significantly higher in

Table 2: Gender, anthropometric, clinical and biochemical variables according to uric acid serum levels among 81 obese adolescents

	---------- Uric acid categorize ----------			
Variables	Hyperuricemia (n = 55)	Normal (n = 26)	PR (95% CI)	P
Gender				
Male	32 (39.5)	9 (11.1)	2.63 (0.99-6.93)	0.048[a]
Female	23 (28.4)	17 (21.0)		
WC				
Increased	32 (39.5)	12 (14.8)	1.62 (0.63-4.15)	0.310
Normal	23 (28.4)	14 (17.3)		
NC				
Increased	39 (48.1)	14 (17.3)	2.09 (0.79-5.49)	0.132
Normal	16 (19.8)	12 (14.8)		
SBP				
SBP>125 mmHg	20 (34.7)	8 (9.9)	1.29 (0.47-3.48)	0.621
SBP<125 mmHg	35 (43.2)	18 (22.2)		
DBP				
DBP>75 mmHg	30 (37.0)	14 (17.3)	1.03 (0.40-2.62)	0.953
DBP<75 mmHg	25 (30.9)	12 (14.8)		
TG				
Altered	14 (17.3)	0 (0.0)	-	-
Normal	41 (50.6)	26 (32.1)		
HDL-c				
Low	39 (48.1)	18 (22.2)	1.08 (0.39-2.99)	0.877
Normal	16 (19.8)	8 (9.9)		
FBG				
Altered	0 (0.0)	1 (1.2)	-	-
Normal	55 (67.9)	25 (30.9)		
MetS				
Present	29 (35.8)	5 (6.2)	4.68 (1.54-14.21)	0.004[a]
Absent	26 (32.1)	21 (25.9)		

CI: Confidence interval, WC: Waist circumference, NC: Neck circumference, PR: Prevalence ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides, HDL-c: High density lipoprotein, MetS: Metabolic Syndrome. [a]Chi Squaare p-values

Table 3: Adjusted odds ratio (95% confidence interval) of alterations in uric acid in 81 obese adolescents

Dependent	Variables	Adjusted OR	Adjusted p-value (95% CI)	p-value hosmer and lemeshow
Hyperuricemia	Gender (male vs. female)	1.92	0.209 (0.69-4.39)	0.697[a]
	Presence of metabolic syndrome	3.97[b]	0.018 (1.27-12.41)	

[a]Logistic regression model fit (p-value Hosmer and Lemeshow>0.05),

[b]The presence of metabolic syndrome has been risked to Hyperuricemia 3.97 higher than without metabolic syndrome

accordance with the number of risk factors that exist in the metabolic syndrome (Pacifico *et al*., 2009).

Uric acid levels could be developed as a sensitive marker of metabolic syndrome (Zhang *et al*., 2013). Increasing of UA levels administered low-degree inflammation, insulin resistance and metabolic syndrome by MCP-1 activation and decreased in adiponectin. MCP-1 is an inflammatory cytokine that might be over expression in metabolic syndrome induced by oxidative stress. Obesity was contributed to adipose tissue oxidative stress (Baldwin *et al*., 2011). Previous study *in vivo* and *in vitro* conducted by Zhu *et al*. (2014) showed mechanisms of hyperuricemia impaired insulin sensitivity through direct mechanisms. Hyperuricemia could directly inhibited insulin alert to liver and fat tissue. It promoted oxidative stress as the important role in mechanism of hyperuricemia-insulin resistance (Zhu *et al*., 2014).

In future, prevalence of the MetS in Indonesian adolescents is estimated to increase along with the increasing prevalence of obesity and lifestyle changes, where it would increase the incidence of insulin resistance. Furthermore, it is known that there is a direct relationship between hyperuricemia and insulin resistance. Hyperuricemia induced insulin resistance as a marker of the MetS with various consequences (Manzato, 2007). On histologic examination of kidney tissue found a dramatic increase in renal parenchymal infiltration by macrophages that showed high levels of uric acid. Increased levels of uric acid that has triggered inflammation of the kidneys, activating the renin-angiotensin system and reduce the production of NO which are all important pathways the uric-acid-mediated hypertension (Nakagawa *et al*., 2006).

Increasing of uric acid was an independent risk factor in diabetes mellitus both in men and women, furthermore a meta-analysis reported that high levels of uric acid as an independent risk factor for metabolic component in middle age (Lv *et al*., 2013). Likewise, hyperinsulinemia and hyperuricemia have an influence one to another. However in this study, we did not investigate HOMA IR due to limitation of resources.

Conclusion: Examination of uric acid should be considered although without any signs and symptoms of gout because UA is a modifiable risk factor of metabolic syndrome.

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